REMARKS

This application is a divisional application of Application No. 09/039,260, filed on March 16, 1998, which is currently pending; which is a divisional application of Application No. 08/783,393, filed January 13, 1997, which issued as U.S. Patent No. 5,731,319; which is a divisional application of Application No. 08/366,651, filed December 30, 1994, which issued as U.S. Patent No. 5,595,997.

Claims 34 to 42 are currently pending in the application for the Examiner's review and consideration. Claim 35 has been amended to more clearly recite the claimed embodiment by stating that the method treats urticaria and further reduces or avoids adverse effects associated with other non-sedating antihistamines. *See* Specification at page 12, lines 16-21. Claim 37 has been amended to more clearly recite the claimed invention by replacing the term "DCL" with "descarboethoxyloratidine." Claim 41 and 42 have been added to recite subject matter previously encompassed by dependent claim 35 as two new dependent claims. Support for the amendments can be found in the application as originally filed. No new matter has been added by these amendments. No fee is believed due for these amendments.

I. The Rejections Under 35 U.S.C. §112, Second Paragraph, Have Been Obviated

Claims 35, 36, and 37 were rejected under 35 U.S.C. § 112, second paragraph, on pages 2-3 of the Office Action as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicants regard as the invention. The Examiner alleges that claims 35, 36, and 37 provide for a further limitation of a method, but since the noted claims do not set forth any steps, it is unclear what changes in the method of claim 34 are intended. Applicants respectfully traverse this rejection.

As the Examiner is aware, "a claim that makes reference to a preceding claim to define a limitation is an acceptable claim construction [unless]. . . where the format of making reference to limitations recited in another claim results in confusion." *See* Manual of Patent Examining Procedure ("M.P.E.P.") § 2173.05(f). Applicants have used such an acceptable claim construction.

Claim 34 recites, in part, a method of treating urticaria comprising the administration of DCL to a human in need thereof. Claim 35 further requires that the method of claim 34 not only treat urticaria but also reduce or avoid adverse effects associated with the

administration of non-sedating antihistamines. Claim 36 further limits claim 34 to a method wherein the recipient is a human who has higher than normal propensity for or incidence of cancer. Claim 37 further limits claim 34 in that the administration of DCL avoids an interaction between DCL and a drug that inhibits cytochrome P450.

Applicant respectfully submits that claims 35, 36, and 37 would not result in confusion, and these claims are properly dependent upon independent claim 34. Applicants respectfully request that the rejection of these claims under 35 U.S.C. § 112, second paragraph, be withdrawn.[1]

II. The Rejections Under 35 U.S.C. §103(a)

Claims 34-40 remain rejected under 35 U.S.C. § 103(a) as being obvious over *The MERCK MANUAL of Diagnosis and Therapy*; 1992, pp. 332-334 to Berkow *et al.* ("Berkow") in view of U.S. Patent No. 4,659,716 to Villani *et al.* ("Villani") for the reasons set forth on pages 3-5 of the Office Action. Applicants respectfully traverse this rejection.

As the Examiner is well aware, three basic criteria must be met to establish a case of *prima facie* obviousness: first, there must have been at the time of the invention a motivation to combine the references cited; second, the alleged prior art must teach or suggest all of the limitations of the claims alleged to be obvious; and third, there must have been at the time of the invention a reasonable expectation of success. MPEP § 2142. In addition, a *prima facie* case of obviousness may be rebutted by showing that the claimed invention achieves unexpected results or by showing that the art teaches away from the claimed range. MPEP § 2144.05(III).

The pending claims recite, in part, a method of treating urticaria in a human in need thereof, which comprises administering a therapeutically effective amount (*e.g.*, from about 0.1 mg to about 10 mg per day) of descarboethoxyloratadine (DCL) or a pharmaceutically acceptable salt thereof. Applicants respectfully submit that the cited art, as discussed below, does not disclose or suggest the claimed invention, much less provide the legally required reasonable expectation of success.

The Examiner alleges that Villani teaches that DCL and related compounds are known to be antihistamines, and the disclosure by the Applicants that DCL is useful in the

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[1] However, if the Examiner wishes to suggest further claim language, Applicants will consider such language.

treatment of urticaria has the expected effect as predicted by Berkow. The Examiner further alleges that the failure of the Applicants to establish any unexpected results, when taken together with the instant combination of references renders the instant claimed subject matter lacking in patentable distinction over the prior art. Applicants respectfully traverse the rejection for the reasons set forth below.

The primary reference, Berkow, discloses that symptoms of acute urticaria usually can be relieved with oral first generation anti-histamines, such as diphenhydramine, hydroxyzine, or cyprohependine.[2] *See* Berkow, Page 333. Berkow does not however disclose or suggest the use of any second generation non-sedating antihistamines, much less DCL to treat urticaria. In addition, hydroxyzine (one of the agents Berkow suggests to treat urticaria) has been reported to induce urticaria rather than treat it. *See* Michel *et al.*, Skin Reactions to Hydroxyzine, *Contact Dermatitis*, **1997**, *36*, 147-149 ("Michel") (attached hereto as Exhibit C).[3] The Michel reference would therefore at the very least impart confusion in the art, if not refuting the disclosure of Berkow concerning the possible use of hydroxyzine against urticaria, altogether.

More importantly, it has been shown that certain types of urticaria do not respond at all to antihistaminic drugs. *See* Parslew *et al.*, Warfarin Treatment of Chronic Idiopathic Urticaria and Angio-Oedema, *Clinical and Experimental Allergy*, **2000**, *30*, 1161-1165 (attached hereto as Exhibit D). Such art is directly contrary to Berkow and must be considered by the Examiner. Indeed, a proper analysis under § 103 requires consideration of the scope and content of the art. M.P.E.P. § 2141 citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966). When proper consideration is given to the art as a whole, it is clear that the contention that Berkow suggests that DCL can be expected to treat urticaria is meritless.

Villani does not remedy the deficiencies of Berkow. Villani discloses a class of compounds of the type: 7- or 8-(halo)-substituted-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridines, encompassing literally hundreds of compounds. *See*

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[2] The use of first generation antihistamines was limited by their activation of muscarinic, cholenergic, serotonergic, or alpha-adrenergic receptors, leading to unwanted side-effects. *See* Simons, The Pharmacology and Use of H_1 Receptor-Antagonist Drugs, *New England Journal of Medicine*, **1994**, *330*, 1663-1670.

[3] Applicants have also cited references in a Second Supplemental IDS to ensure consideration by the Examiner. Such citation by Applicants is not an admission that any or all references are prior art.

Col. 1, lines 17-38. Although Villani alleges this class of compounds can be shown to have antihistaminic activity, Villani does not disclose or even suggest the treatment of urticaria with any of its compounds, much less treating urticaria with DCL.

The cited references when combined at most merely suggest that each of the numerous compounds disclosed by Villani be tried in a method of treating urticaria.[4] However, it is well established that an allegation that a claimed invention may have been "obvious to try" does not satisfy the requirements that must be met to establish a case of *prima facia* obviousness. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d 1367, 1380 (Fed. Cir. 1986).

In sum, Berkow merely suggests treating the symptoms of urticaria with a first generation sedating antihistamine, and Villani only discloses treating allergic reactions using second generation antihistamines and says nothing about urticaria. Further neither reference alone or in combination discloses or suggests a method of treating urticaria, while reducing or avoiding adverse effects associated with non-sedating antihistamines. As the Examiner is aware, in order to form a proper basis for a rejection under 35 U.S.C. § 103, the prior art must provide some suggestion, either explicit or implicit, of the combination that allegedly renders a claimed invention obvious. MPEP § 2142. This suggestion is absent from the cited references.

Even though Applicants have clearly established that the cited references do not establish a *prima facia* case of obvious, they reiterate that the Examiner must also consider that at the time of the invention it was known that the administration of second generation antihistamines, although free from certain side-effects associated with administration of first generation antihistamines, was reportedly associated with the risk of severe dysrhythmias. *See* Yap *et al.*, The Current Cardiac Safety Situation With Antihistamines, *Clinical and Experimental Allergy*, **1999**, *29*, 15-24. (Attached hereto as Exhibit E). Specifically, non-sedating antihistamines such as terfenadine and astemizole are known to cause certain, sometimes severe, adverse effects. In particular, they are known to induce cardiac arrhythmias. It was known that, these non-sedating antihistamines should not be coadministered with medications that inhibit cytochrome P450 activity, because drug

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[4] Applicants do not concede that it is proper to combine these references. Indeed, there is no motivation to combine them at least because they do not even relate to the same class of antihistamines nor the same diseases.

interactions have been associated with cardiac arrhythmias. *See Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed. 1996, pp. 1607. Although second generation antihistamines lack certain adverse effects associated with first generation antihistamines (*e.g.*, anticholenergic activity), these compounds, at the time the invention, were becoming increasingly disfavored due to their inherent cardiotoxicity.

More importantly, skin reactions to certain second generation antihistamines have been reported, further disfavoring their administration, especially for treating urticaria (also a skin reaction). *See* McClintock *et al.*, Skin Reactions and Terfenadine, *New Zealand Medical Journal*, **1995**, *108*, 208. (Attached hereto as Exhibit F). As shown above it can be further demonstrated that at the time of the invention the art taught away from using second generation antihistamines to treat urticaria due to the potential for cardiotoxicity and the potential for adverse skin reactions after administration of these anthistamines.

Thus, one of ordinary skill in the art would not read the suggestion in Berkow "to try" first generation antihistamines as a suggestion to try second generation antihistamines, which are known as a class to have different risks and benefits Indeed, one of ordinary skill in the art would have no motivation to even try second generation, non-sedating antihistamines to treat urticaria. In fact, the state of the art at the time of the invention actually teaches away from using first or second generation antihistamines to treat urticaria, since it was reported that both classes of antihistamines were either ineffective in treating urticaria or actually induced urticarial outbreaks upon administration. *See* Michel supra. *See also* Monroe, Loratidine in the Treatment of Uriticaria, *Clinical Therapeutics*, **1997**, *19*, 232-242. (Attached hereto as Exhibit G).

Finally, the Examiner has alleged that the Applicants fail to establish any unexpected results. Applicants respectfully direct the Examiner's attention to the Example section of the specification. The Examples describe the therapeutic activity of DCL, while avoiding or reducing adverse effects associated with other second generation antihistamines. This is particularly important in view of the fact that at the time prior to the claimed invention, compounds of the class of non-sedating antihistamines (*e.g.*, loratidine, terfenadine, astemizole) were known to cause or have a potential for severe adverse effects, such as ventricular fibrillation, cardiac arrhythmias, and tumor growth. This application describes a variety of surprising and unexpected benefits encompassed by the claimed invention. For Example, Example 4 illustrates that DCL is 5-7 fold less active than loratidine

at promoting tumor growth. *See* Specification at Page 24. Example 5 demonstrates that DCL is less active than terfenadine in inhibiting the cardiac delayed rectifier and thus has no potential for cardiac side-effects. *See* Specification at Pages 24-26. Such results are evidence of unexpected results that can rebut even a *prima facia* case of obviousness.

Conclusion

Neither Berkow nor Villani taken alone or in combination suggest a method of treating urticaria, which comprises the administration of a second generation antihistamine, much less a method using DCL. Neither reference taken alone or in combination provides the required reasonable expectation of successfully arriving at the claimed invention. Indeed, at the time of the invention a reasonable expectation of success could not exist since (a) the state of the art was confused as to what types of drugs were useful in treating urticaria; and (b) second generation non-sedating antihistamines were believed to even cause urticaria in some instances. Finally, the specification provides data that is contrary to the Examiner's contention of obviousness.

Applicants therefore respectfully request that the rejection of claims 34-40 under 35 U.S.C. § 103 be reconsidered and withdrawn.

Should any additional fees be required, however, please charge such fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

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Enclosures

35. (Twice Amended) The method of claim 34, which further comprises reducing or avoiding [an] adverse [side] effects associated with non-sedating antihistamines [effect selected from the group consisting of including cardiac arrhythmia and tumor promotion].

37. (Twice Amended) The method of claim 34, which further comprises avoiding an interaction between descarboethoxyloratadine (DCL) [DCL] and a drug that inhibits cytochrome P450.

48 ~~41~~. (New) The method of claim 35, wherein the adverse effects is cardiac arrhythmia.

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49 ~~42~~. (New) The method of claim 35, wherein the adverse effects is tumor promotion.

34. (Twice Amended) A method of treating urticaria in a human comprising administering to a human in need thereof a therapeutically effective amount of descarboethoxyloratadine (DCL) or a pharmaceutically acceptable salt thereof.

35. (Twice Amended) The method of claim 34, which further comprises reducing or avoiding adverse effects associated with non-sedating antihistamines.

36. The method of claim 34 wherein said human has a higher than normal propensity for or incidence of cancer.

37. (Twice Amended) The method of claim 34, which further comprises avoiding an interaction between descarboethoxyloratadine (DCL) and a drug that inhibits cytochrome P450.

38. (Amended) The method of claim 34 wherein the amount of descarboethoxyloratadine (DCL) administered is from about 0.1 mg to less than about 10 mg per day.

39. (Amended) The method of claim 38 wherein the amount of descarboethoxyloratadine (DCL) administered is from about 0.1 mg to less than about 5 mg per day.

40. (Amended) The method of claim 34 wherein the amount of said descarboethoxyloratadine (DCL) or a pharmaceutically acceptable salt thereof is administered together with a pharmaceutically acceptable carrier.

41. (New) The method of claim 35, wherein the adverse effect is cardiac arrhythmia.

42 (New) The method of claim 35, wherein the adverse effect is tumor promotion.